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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,140	05/30/2007	Joseph D. Buxbaum	7703/9	1982

1912 7590 05/11/2010

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EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
05/11/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,140	BUXBAUM ET AL.	
	Examiner	Art Unit	
	SARAE BAUSCH	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/09/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to applicants correspondence mailed 01/04/2010. The amendment to the claims mailed 06/17/2009 and the amendment to the specification mailed 01/04/2010 has been entered.

Election/Restrictions

2. Applicant's election with traverse of group I in the reply filed on 06/17/2009 is acknowledged. The traversal is on the ground(s) that groups I-III would not be an undue burden for the examiner to consider. This response has been review and found persuasive. The restriction requirement between groups I-III has been withdrawn however the restriction requirement between groups I-III and IV-V is maintained.

The requirement is still deemed proper and is therefore made FINAL.

3. Currently claims 1-3, rs2056202, rs2292813, and the combination of rs2056202 and rs2292813 are under examination.

Drawings

4. The drawings are acceptable.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite. Claim 1 is drawn to a method of evaluating an individual for relative genetic risk for autism, however the process step encompasses only wherein the presence of a G at either of the two sites indicates an increased risk for autism. Accordingly the claims are ambiguous and incomplete, omitting essential steps. There is an omitted step, for example a correlation between determining the genotype and relative genetic risk for autism. There is no nexus between the preamble and the process steps and it is not clear that the determining the genotype will necessarily result in evaluating an individual for relative genetic risk for autism. Therefore claim 1 is indefinite because the limitation in the preamble is not recited in the process steps, the metes and bounds of the claim are vague and indefinite, and it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s).

Claim Rejections - 35 USC § 112- Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to method for identifying relative genetic risk for autism in an individual comprising determining the genotype at polymorphism sites rs2056202 and/or rs2292813.

The claims encompass analysis of relative genetic risk for autism and identifying polymorphisms at sites rs2056202 and rs2292813 in any individual, human or non-human.

The nature of the invention, therefore, requires the knowledge of a robust and reliable correlation between association between the polymorphisms rs2056202 and rs2292813 and susceptibility to autism in any individual, human or non-human.

Guidance in the Specification and Working Examples

The specification asserts an association between increased risk of autism in individuals having a G allele at either or both polymorphism sites rs2056202 and rs2292813 of SLC25A12 gene. The specification asserts identifying rs2056202 and rs2292813 and genotyping 411 autistic families, including linkage and association tests carried out in 197 informative families. The specification asserts that linkage and association between autistic disorder and rs2056202 and rs2292813 was observed (see pg. 9, example 1). The specification asserts that the evidence for association of rs2056202 and rs2292813 in a small number of cases and controls was determined (See pg. 13). Table 1 demonstrates that rs2292813 was not associated with paternal transmission nor was the haplotype G*A associated in table 1 or table 2. The specification teaches that with all association studies especially complex disorders thought to be due to multiple interacting genes of weak effect such as autism, replication in independent samples must be completed before the results can be accepted. The specification teaches that the study presented lacks power, where many of the parents were homozygous at the two loci and a carefully designed case-control study with control matched for ethnicity, gender and age may have more power to detect association at these two loci or alternatively genotyping several hundred trios for TDT would be in order for a replication study (See pg. 18 last paragraph cont'd to page 19). Furthermore the specification teaches that the susceptibility variants are common alleles which would not be immediately useful for genetic counseling until it can be considered together with additional loci (see pg. 19, lines 8-14).

Thus the specification demonstrates the unpredictability of the association rs2056202 and rs2292813 with risk of autism in any individual, human or non-human and demonstrates the

need for replication studies to validate the data presented in the specification. The specification demonstrates the unpredictability by teaching that susceptibility allele, G at position rs2056202 and rs2292813 is the common allele and would not be useful for genetic counseling until further studies are replicated, including carefully designed case-control studies and studies with more power.

The state of the prior art and the predictability or unpredictability of the art:

There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. However, the art exemplifies the unpredictability with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a

genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789).

Because the claims are drawn to methods comprising the analysis of non-humans, whereas the instant specification provides only data generated from human subjects, it is relevant to point out the unpredictability with regard to extrapolating data among different species. It is possible that an apparent polymorphism site, rs2056202 or rs2292813 in the SLC25A12 gene in a non-human organism might not be equivalent, with regard to risk of autism, to the homologous gene in humans. Such a possibility is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S). Thus, even if homologs of the SLC25A12 genes were analyzed in other organisms, one would have to perform a large amount of experimentation to determine whether or not these genes would be useful in predicting risk of autism in any non-human organism. The unpredictability of interspecies sequence comparison is

further demonstrated in the prior art of Mummidi et al (2000). Mummidi et al teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that substantial interspecies sequence variation is observed (p.18949, right col., first full para).

At the time the invention was made, the art was silent with regard the presence of a G allele at position rs2056202 and rs2292813 of SLC25A12 association with increased risk of autism. The specification teaches that replication studies are necessary to validate the association of rs205602 and rs2292813 and risk of autism, as the study presented in the instant application is under powered and since the susceptibility alleles are the common allele would not be immediately useful for genetic counseling (see pg 19). The post filing art teaches that in replication studies the G allele of rs2056202 and rs2292813 of the SLC25A12 gene was not associated with risk of autism. Chien (Progress in Neuro-Psychopharmacology and Biol Psych, 2010, vol 34, pp 189-192) teaches genotyping rs2056202 and rs2292813 of 465 patients with autism and 450 control subjects from Taiwan (see methods). Chien demonstrates that the SLC25A12 gene is not associated with autism in their population. Chien teaches that genetic associations are well known for their inconsistent results among different studies and teach that clinical heterogeneity of patients, including different research groups recruiting patient with different severity of symptoms and varied symptom dimensions, however their study included only autistic disorder. Chien teaches their study is the largest sample size in a genetic study of the SLC25A12 and autism in the literature and even this sample size has limited power and teaches that larger sample size or meta-analysis is needed to address the association of SLC25A12 gene and autism (see pg. 193). Correia (J Autism Dev Disord 2006, 36:1137-1140)

teaches testing the association of rs2056202 with autism (see pg. 1138). Correia demonstrate that rs2056202 in their population was not associated with autism and suggest that different physiological mechanism may be involved and teach that additional population will be required for a definite conclusion (see pg. 1139). Rabionet et al. (Am J Psychiatry, 2006, 163:929-931) demonstrates an independent study of 327 families with autistic offspring to test the association of SNPs rs2056202 and rs2292813. Rabionet teaches genotyping alleles and haplotypes including sites rs2056202 and rs2292813 of the SLC25A12 gene and concludes there is no evidence of an association between SLC25A12 and autism (see results). Rabionet teaches that no association was found for individual SNPs, haplotypes, or families with positive lod scores (see pg. 930). Rabionet teaches that population differences could account for the different results or the associated described by applicants own work could be caused not by a variation in SLC25A12 but a variation nearby gene or that association could be due to a type I error. Blasi (Eu. J. Human Gen. 2006, 14:123-126) demonstrates that SLC25A12 is not associated with autism in a multiplex family sample. Blasi demonstrates that SNPs rs2292813 and rs2056202 was not found to be associated with autism and not likely to contribute strongly to autism susceptibility (see pg. 125).

As exemplified by the post filing date art, a large amount of unpredictability exists regarding the association of SNPs at polymorphic position rs2056202 and rs2292813 in the SLC25A12 gene and autism. As taught in the specification, replication studies are needed to determine the validity of the association and as demonstrated by the post filing art (Chien, Rabionet, Blasi) autism is complex disease and population differences may account for different association results, thus demonstrating the unpredictability of SNP association studies and

specifically demonstrating the unpredictability of associating increased risk of autism with the presence of a G allele at either or both polymorphic positions, rs2056202 and rs2292813, of the SLC25A12 gene in any individual, human and non-human.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

To practice the invention as broadly as it is claimed, the skilled artisan would have to perform a replication study of a large study family based and population based study to predictably determine the association of either or both polymorphic sites rs2056202 and rs2292813 with a G allele and autism in any individual, human or non-human. The art confirms the need for such study, as well as teaching that the outcome of such study is unpredictable as several replication studies were unable to reproduce that the presence of a G allele at position rs2056202 or rs2292813 is associated with autism.. The assessment of polymorphisms with regard to phenotypes and disease states, particularly complex diseases such as autism is highly unpredictable. Given the polymorphic nature of genomic DNA as well as the fact that different populations of people possess different combinations of specific alleles, large population based studies are required to accurately assess the identity of any particular SNP in terms of association to disease state or phenotype, especially in complex diseases such as autism. The experimentation required by the skilled artisan to make and use the instant invention, as broadly

as it is claimed, would be replete with unpredictable trial and error analysis, with many intervening steps requiring a large amount of inventive effort. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the conflicting data provided in the specification, the lack of guidance in the prior art as well as the teachings and examples of unpredictability in the post filing date art, balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the methods of the claims as broadly written.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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/Sarae Bausch /
Primary Examiner, Art Unit 1634